REMARKS

Claims 68-83 and 107-114 are pending. The claims are directed to methods of relieving keratoconjunctivitis sicca (Dry Eye Syndrome) -associated ocular inflammation that cause patient discomfort, e.g., in the form of itching, burning irritation, redness. Dry Eye Syndrome, a disorder that involves the quality of the tear film that lubricates the eye, is one of the most common problems treated by eye physicians. As is disclosed in the specification, reactive oxygen species (ROS) and inflammatory mediators (e.g., phospholipase A2 (PLA-2), cytokine –inducible nitric oxide synthetase (iNOS), inducible cyclooxegenase (COX-2), eosinophils and cAMP-phosphodiesterase) are among the underlying causes of the pathogenesis of Dry Eye. The method of the invention requires administration (preferably orally) of a combination of key compounds – a carotenoid, comprising astaxanthin (one of the strongest naturally occurring free radical scavengers known) and a polyphenol with co-administration of an omega-2 fatty acid. The polyphenol comprises curcuma longa root powder, green tea, grape seed extract, or a citrus bioflavonoid. Polyphenol COX-2 inhibitors include quercetin, a bilberry extract, a hops PE, blueberry powder or tart cherry powder. Co-administration of an omega-3 fatty acid, e.g., eicosapentaenoic acid or docosahhexaenoic acid, inhibits pro-inflammatory mediators.

A clinical trial using this combination of key compounds formulated into an ocular protective combination (OPC) formulation showed surprising results in alleviating inflammation associated with Dry Eye, and patients reported a reduction in the severity of symptoms associated with the condition. The striking level of reduction of patient discomfort and significant decrease in objective indicia of ocular inflammation combined with a favorable safety profile makes the OPC combination formulation ideal for patients with Dry Eye Syndrome (see Declaration of Dr. Steven G. Pratt, which is of record in this case). The only remaining issue of patentability is a rejection for obviousness based on a combination of three references, two of which were cited in the previous office action.

35 U.S.C. §103

Claims 68-83 and 107-114 were rejected under 35 U.S.C. 103 (a) as being unpatentable over Gorenbein et al. (USPN 6,200,601) in view of Petrus (USPN

6,573,299) and further in view of Thomas (US 5,811,446) for the reasons set forth on pages 5-8 of the office action of November 12, 2009 and the following reasons.

> On page 2 of the Office Action, the Examiner states:
>
> Thomas teaches the use of astaxanthin in an ophthalmic formulation in combination with other active ingredients for protecting eye from various eye conditions and the treatment of inflammation resulting from various causative agents. See the abstract, claims 28 and 30. The above reference makes clear that astaxanthin has been previously used in an ophthalmic formulation for the treatment of inflammation and protecting eye from various eye disorders.
>
> Applicant's arguments and remarks have been carefully considered, but are not deemed to be persuasive. Applicant in his remarks argues the use of astaxanthin instead of zeaxanthin taught by the prior art. Such arguments in view of the newly relied upon reference are considered to be moot.

Gorenbein and Petrus were discussed in the previous response filed on May 12, 2010. The Examiner has now applied a new reference, Thomas, apparently for the sole purpose of describing of "astaxanthin" in the context of the eye. As was discussed in the previous response, the Gorenbein reference does not disclose astaxanthin. Gorenbein also fails to describe or suggest the condition of Dry Eye Syndrome or even inflammation. Instead, Gorenbein is entirely focused on supplements "for improving night vision acuity, field of vision and adaptation to light". The secondary reference, Petrus, also fails to describe or suggest Dry Eye, and the term "astaxanthin" does not appear in this reference either. The Petrus reference is concerned with orbital disorders, e.g., cataracts, glaucoma, diabetic retinopathy and macular degeneration, as well as age-related changes to the eyelids such as dry skin, wrinkles, keratoses, age spots and pigmented skin lesions. The specific diagnostic indication of Dry Eye is present in neither Gorenbein nor Petrus. The composition, astaxanthin, was not disclosed in Gorenbein or Petrus. Thus, the combination of Gorenbein and Petrus cannot support an obviousness rejection of the pending claims.

The Thomas reference describes administration of the amino acid, histidine, for prophylaxis of an extensive list or specific "diseases or degenerations" ("glaucoma, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), corneal amyloidosis, age-related macular

degeneration, retinal photic injury, retinal ischemia-induced eye injury, and free-radical-mediated diseases and/or injuries, Dellen, Terrein's Marginal Degeneration, and calcific band keratopathy") as well as inflammation arising from such disease states as well as surgical, chemical, or accidental physical trauma. Thomas states that histidine is preferably administered topically or orally, or by both routes – and describes co-administration of histidine with another long list of therapeutic compounds (e.g., antibiotics, antioxidants, antivirals, corticosteroids, non-steroidal anti-inflammatory agents, anti-glaucoma agents, collagenase inhibitors…)

The rejection seems to be based on 3 references, each of which relates to a completely different eye-related condition. Given this disparity, the rejection is based on the premise that any reference describing a compound in the context of treating the eye can be combined with any other reference describing a compound in the context of treating a completely different eye pathology and is tantamount to cherry-picking of compositions from artbitrary eye-related references. This flawed way of thinking about disorders of the eye is perhaps reflected in the Examiner's following statements:

> Thomas teaches the use of astaxanthin in an ophthalmic formulation in combination with other active ingredients for protecting eye from various eye conditions and the treatment of inflammation resulting from various causative agents. See the abstract, claims 28 and 30. The above reference makes clear that astaxanthin has been previously used in an ophthalmic formulation for the treatment of inflammation and protecting eye from various eye disorders.

Applicants submit that the "various eye disorders" described in each of the cited references are not interchangeable. Dry Eye Syndrome is a specific diagnosed condition, and neither Gorenbein, nor Petrus, nor Thomas describes alleviating Dry Eye Syndrome-associated ocular inflammation. One of skill in the ophthalmic arts would not be motivated to treat inflammation associated with dry eye with compositions disclosed for the treatment of , e.g., impaired night vision (Gorenbein) or cataracts, glaucoma, diabetic retinopathy, macular degeneration, and dry eyelid skin (Petrus).

The tertiary reference, Thomas, concerns yet another set of eye pathologies – "diseases or degenerations" ("glaucoma, diabetic retinopathy, disease-based posterior vitreous detachment (PVD), age-based posterior vitreous detachment (PVD), corneal

amyloidosis, age-related macular degeneration, retinal photic injury, retinal ischemia-induced eye injury, and free-radical-mediated diseases and/or injuries, Dellen, Terrein's Marginal Degeneration, and calcific band keratopathy") as well as inflammation arising from such disease states as well as surgical, chemical, or accidental physical trauma as well as ocular inflammation specifically as a result of or secondary to tissue damage caused by acute injury or infection by a bacteria, virus, or parasite. Treatment of the specific disorder, Dry Eye Syndrome, is not described or suggested by this reference. Specifically, the reference describes the use of the amino acid histidine to treat the pathologies listed. Histidine is sometimes disclosed as being co-administered with one or more of a long list of compositionsincluding "a carotenoid (such as astaxanthin, canthatzanthin, β-carotene, zeaxanthin, lutein and α-tocopherol)". In no way does Thomas suggest administering astaxanthin in the absence of histidine.

Given the disparity in the conditions described by each of these references, one of skill in the art would not be motivated to combine their teachings. The combination of references used to support the obviousness rejection could only have been identified by impermissible use of hindsight.

Applicants submit that independent claim 68 and those claims, which depend from claim 68 are non-obvious in view of the cited combination of references. Applicants further note that none of the references describe or suggest all of the elements (ingredients of the OPC composition) recited in claims 108-114; thus, the rejection for obviousness of these claims cannot stand. Morever, the results of the clinical trial as described in the Declaration of Dr. Steven G. Pratt and in the Declaration of George Ousler provide evidence of suprising results in the success of the methods. This evidence weighs in favor of non-obviousness. Withdrawal of the rejection under §103 is therefore respectfully requested.

CONCLUSION

Applicants believe that the application and claims are in condition for allowance. The Examiner is invited to contact the undersigned at the number or email listed below should she believe that there are any remaining issues that could be more easily resolved by personal or telephonic interview.

Applicants submit herewith a Petition for a Three-Month Extension of Time, together with an electronic payment in the amount of $555.00. The Commissioner is hereby authorized to charge any additional fees that may be due, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 41108-503002US (formerly: 21534-002CIP).

Respectfully submitted,

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